IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Kohichi TANAKA et al.
Title:	MOUSE DEFICIENT IN GLUTAMATE TRANSPORTER GLAST FUNCTION
Appl. No.:	10/553,051
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Examiner:	Fereydoun G. SAJJADI
Art Unit:	1633
Confirmation Number:	5841

DECLARATION UNDER 37 CFR§ 1.132

Commissioner for Patents
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I, Kohichi Tanaka, hereby declare:

1. I, Kohichi Tanaka, am an inventor of the above identified Application. My curriculum vitae is attached as **APPENDIX A**, including details of my experience and background.

2. I have read and understood the Office Action dated June 20, 2008, and particularly the Examiner's comments regarding the alleged obviousness for a person of ordinary skill in the art to combine the teaching of Watase et al. and Chitnis et al.

3. In response to the Examiner's above comments, I hereby provide the following information which demonstrates that it is, indeed, a surprising result that the method disclosed in this Application produces GLAST knockout mice having an intraocular pressure within a normal range (not greater than 21 mmHg) and having at least 20% less retinal ganglions cells than a wild-type mouse.

Figure 1A

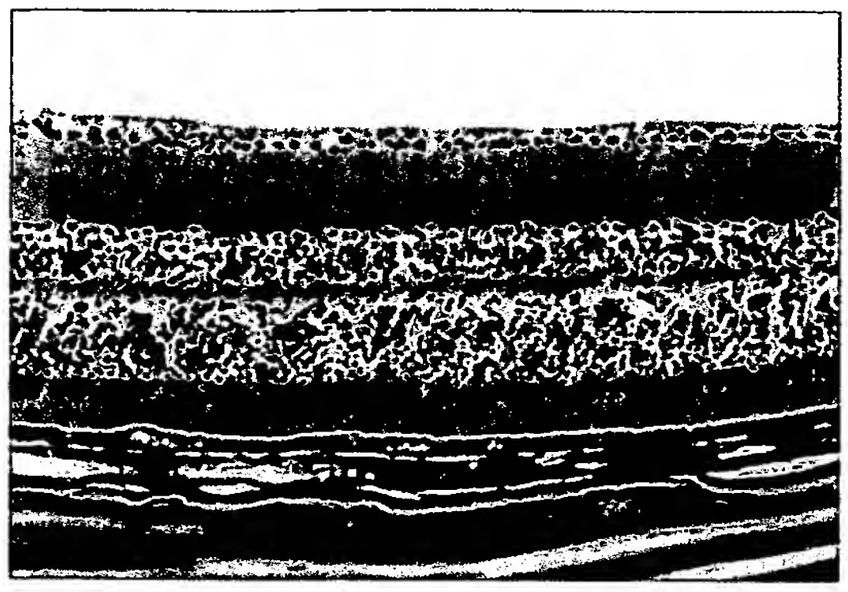


Figure 1B

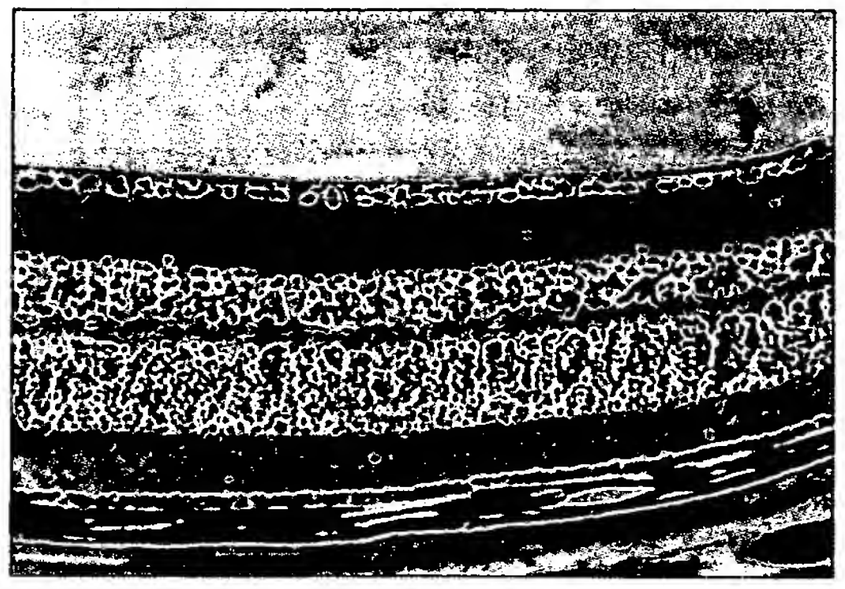
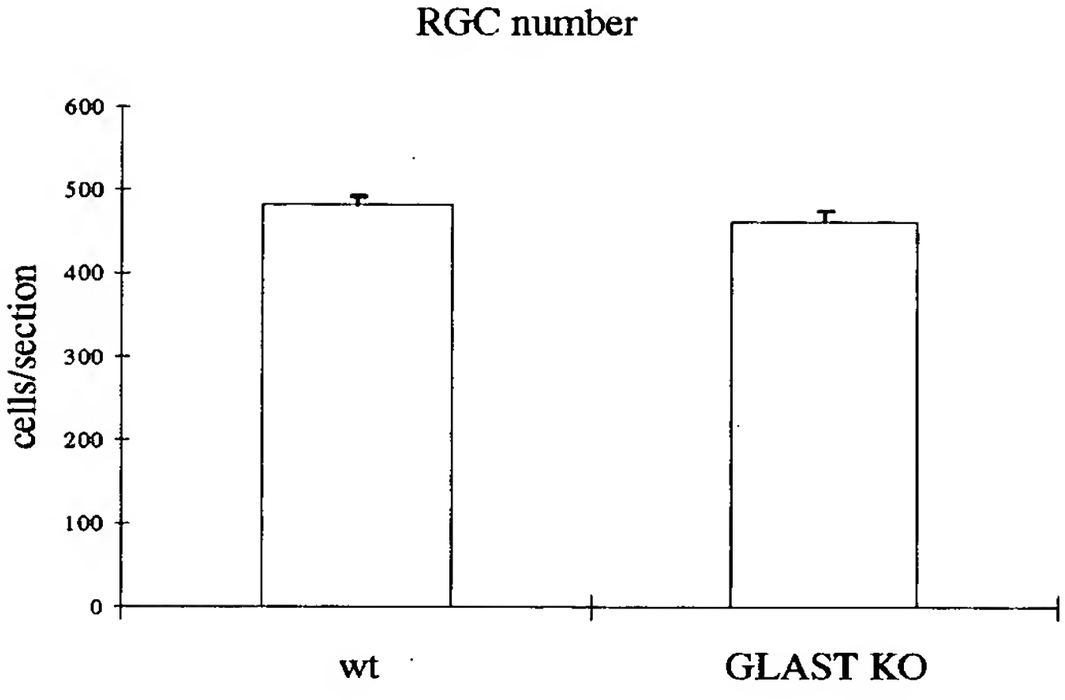


Figure 2



4. In a comparative experiment, the GLAST knockout mice were backcrossed with 129sv strains, instead of C57BL/6J strains as disclosed in the Application. The conditions of the comparative experiment are similar to that of the experiments previously described in the Specification, except that 129sv strains, instead of C57BL/6J strains, were used for backcrossing. Resulting mice were deeply anesthetized with diethylether and perfused transcardially with saline, and then treated by a 4% paraformaldehyde in 0.1 M phosphate buffer containing 0.5% picric acid at room temperature. The eyes of treated mice were removed and postfixed overnight in the same fixative and then were embedded in paraffin. Histological sections, around 7 μm thick, were prepared along the vertical meridian, mounted, and stained with hematoxylin and eosin. Images of histological sections of a wild type mouse and of a GLAST knockout mouse resulting from backcrossing with 129sv strains for ten times are shown in Figures 1A (a wild type mouse) and 1B (a GLAST knockout mouse resulting from backcrossing with 129sv strains), respectively.

5. As shown in Figure 2, the numbers of the retinal ganglion cells (RGC) were counted from one ora serrata through the optic nerve to the other ora serrata, demonstrating that *no observable* reducing of the number of the retinal ganglion cells was found in a GLAST knockout mouse obtained by backcrossing with the 129sv strains, compared to that of a wild type mouse. This conclusion was confirmed by a two-tailed Student's *t*-test, resulting in a p value of 0.37. Thus, in contrast to GLAST knockout mice obtained by backcrossing with the C57BL/6J strains, significant reducing of the number of the retinal ganglion cells was *not* observed on GLAST knockout mice obtained by backcrossing with the 129sv strains.

6. The above experimental results show that the GLAST knockout mice backcrossed with the 129sv strains display a *different phenotype* from the GLAST knockout mice backcrossed with the C57BL/6J strains.

7. In conclusion, in view of the comparative experiment explained above, one of the ordinary skill in the art would *not* be able to predict that the GLAST knockout mouse backcrossed with the C57BL/6J strains would result in the phenotype recited in the present claims, with a reasonable expectation of success, at the time of the instant invention. Indeed, it is surprising that the step of "repeating crossing the heterozygous mouse with a normal C57BL/6 strain mouse to generate a heterozygous knockout mouse" produces an inbred GLAST knockout mouse *not only* having less genotypic and phenotypic background variation, *but also* having an intraocular pressure within a normal range (not greater than 21 mmHg) and having 20% - 50% less retinal ganglion cells than a wild-type mouse. Neither Chitnis nor any other references to my knowledge suggest such results would be possible.

9. I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

By: Kohichi Tanaka _____ ***Date:*** November 12, 2008 _____

Dr. Kohichi Tanaka

Kohichi Tanaka, M.D., Ph.D.

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Education and Training

Degree/ Year	Institution	Field of Study
M.D./ 1984	Niigata University	Medicine
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Professional/Research Experience

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Publications

1. Karlsson, RM., Tanaka, K., Heilig, M., Holmes, A. Loss of Glial Glutamate and Aspartate Transporter (Excitatory Amino Acid Transporter 1) Causes Locomotor Hyperactivity and Exaggerated Responses to Psychotomimetics: Rescue by Haloperidol and Metabotropic Glutamate 2/3 Agonist. *Biol Pschiatry* 64. 810-814,

2008.

2. Takasaki, C., Okada, R., Mitani, A., Fukaya, M., Yamasaki, M., Fujihara, Y., Shirakawa, T., Tanaka, K., Watanabe, M. Glutamate transporters regulate lesion-induced plasticity in the developing somatosensory cortex. *J Neurosci* 28. 4995-5006, 2008.
3. Kiryk, A., Aida, T., Tanaka, K., Banerjee, P., Wilczynski, G.M., Meyza, K., Knapska, E., Filipkowaski, R.K., Kaczmarek, L., Danysz, W. Behavioral characterization og GLT1(+/-) mice as a model of mild glutamatergic hyperfunction. *Neurotox Res* 13. 19-30, 2008.
4. Nikkuni, O., Takayasu, Y., Iino, M., Tanaka, K., Ozawa, S. Facilitated activation of metabotropic glutamate receptors in cerebellar Purkinje cells in glutamate transporter EAAT4-deficient mice. *Neurosci Res* 59. 296-303, 2007.
5. Komine, O., Nagaoka, M., Watase, K., Gutmann, D.H., Tanigaki, K., Honjo, T., Radtke, F., Saito, C., Chiba, S., Tanaka, K. The monolayer formation of Bergmann glial cells is regulated by Notch/RBP-J signaling. *Dev Biol* 311. 238-250, 2007.
6. Tanimoto, S., Suzuki, M., Ue, T., Okumichi, H., Aoyama, H., Souchelnytskyi, S., Tanaka, K., Agarwal, N., Mishima, H.K., Kanamoto, T. Proteomics in retina of Excitory Acid Carrier 1(EAAC1) knockout mice. *Proteome Science* 5. 13, 2007.
7. Maekawa, F., Nakamori, T., Uchimura, M., Fujiwara, K., Yada, T., Tsukahara, S., Kanamatsu, T., Tanaka, K., Ohki-Hamazaki, H. Activation of cholecystokinin neurons in the dorsal pallium of the telencephalon is indispensable for the acquisition of chick imprinting behavior. *J Neurochem* 102. 1645-1657, 2007.
8. Harada, T., Harada, C., Nakamura, K., Qua, H-M.A., Okumura, A., Namekata, K., Saeki, T., Aihara, M., Yoshida, H., Mitani, A., Tanaka, K. The potential role of glutamate transporters in the pathogenesis of normal tension glaucoma. *J Clin Invest.* 117. 1763-1770, 2007.
9. Takatsuru, Y., Iino, M., Tanaka, K., Ozawa, S. Contribution of glutamate transporter GLT-1 to removal of synaptically released glutamate at climbing fiber-Purkinje cell synapses. *Neurosci Lett* 420. 85-89, 2007
10. Maekawa, F., Komine, O., Sato, K., Kanamatsu, T., Uchimura, M., Tanaka, K., Ohki-Hamazaki, H. Imprinting modulates processing of visual information in the visual wulst of chicks. *BMC Neuroscience* 7. 75, 2006.
11. Pardo, A., Wong, V., Benson, L., Dykes, M., Tanaka, K., Rothstein, J.D., Maragakis, N.J. Loss of the astrocyte glutamate transporter GLT1 modifies disease in $SOD1^{G39A}$ mice. *Exp Neurol* 201. 120-130, 2006
12. Mieda, M., Williams, S.C., Richardson, J.A., Tanaka, K., Yanagisawa, M. The dorsomedial hypothalamic nucleus as a food-entrainable circadian pacemaker. *Proc.*

Natl. Acad. Sci. USA. 103. 12150-12155, 2006

13. Matsugami, RT., Tanemura, K., Mieda, M., Nakatomi, R., Yamada, K., Kondo, T., Ogawa, M., Obata, K., Watanabe, M., Hashikawa, T., Tanaka, K. Indispensability of glutamate transporters GLAST and GLT1 to brain development. *Proc. Natl. Acad. Sci. USA*. 103. 12161-12166, 2006
14. Kiryu-Seo, S., Gamo, K., Tachibana, T., Tanaka, K., Kiyama, H. Unique anti-apoptotic activity of EAAC1 in injured motor neurons. *EMBO J* 25. 3411-3421, 2006
15. Glowatzki, E., Cheng, N., Hiel, H., Yi, E., Tanaka, K., Ellis-Davies, G.C.R., Rothsetin, J.D., Gergles, D.E. The glutamate-aspartate transporter (GLAST) mediates glutamate uptake at inner hair cell afferent synapses in the mammalian cochlea. *J Neurosci* 26. 7659-7664, 2006
16. Takayasu, Y., Iino, M., Shimamoto, K., Tanaka, K., Ozawa, S. Glial glutamate transporters maintain one-to-one synapses by preventing glutamate spillover. *J Neurosci.* 26. 6563-6572, 2006
17. Mori, T., Tanaka, K., Buffo, A., Wurst, W., Kuhn, R., Gotz, M. Inducible gene deletion in astroglia and radial glia-a valuable tool for functional and lineage analysis. *Glia* 54. 21-34, 2006
18. Yamashita, A., Makita, K., Kuroiwa, T., Tanaka, K. Glutamate transporters GLAST and EAAT4 regulate postischemic Purkinje cell death: An in vivo study using cardiac arrest model in mice lacking GLAS T or EAAT4. *Neurosci Res* 55. 264-270, 2006
19. Hasegawa, J., Obara, T., Tanaka, K., Tachibana, M. High density presynaptic transporters are required for glutamate removal from the first visual synapse. *Neuron* 50. 63-74, 2006
20. Iwabuchi, M., Tanaka, K., Ohki-Hamazaki, H. Overexpression of gastrin-releasing peptide receptor induced layer disorganization in brain. *Neuroscience* 138. 109-122, 2006
21. Takatsuru, Y., Takayasu, Y., Iino, M., Nikkuni, O., Ueda, Y., Tanaka, K., Ozawa, S. Roles of glial glutamate transporters in shaping EPSCs at the climbing fiber-Purkinje cell synapses. *Neurosci Res* 54. 140-148, 2006
22. Harada, C., Nakamura, K., Namekata, K., Okumura, A., Tanaka, K., Ichijo, H., Harada, T. Role of apoptosis signal-regulating kinase 1 in stress-induced neural cell apoptosis in vivo. *Am. J. Pathol.* 168. 261-269, 2006
23. Harada, C., Harada, T., Nakamura, K., Sakai, Y., Tanaka, K., Parada, L.F. Effects of $p75^{NTR}$ on the regulation of naturally occurring cell death and retinal ganglion cell number in the mouse eye. *Dev Biol* 290. 57-65, 2006

24. Herard, AS., Dubois, A., Escartin C., Tanaka, K., Delzescaux, T., Hantraye, P., Bonvento, G. Decreased metabolic response to visual stimulation in the superior colliculus of mice lacking the glial glutamate transporter GLT-1. *Eur J Neurosci* 22. 1807-1811, 2005
25. Takayasu Y., Iino, M., Kakegawa, W., Maeno, H., Watase K., Wada, K., Yanagihara D., Miyazaki T., Komine O., Watanabe M., Tanaka, K. Ozawa, S. Differential roles of glial and neuronal glutamate transporters on Purkinje cell synapses. *J Neurosci* 25. 8788-8793, 2005
26. Harada, C., Harada, T., Quah, H-M A., Namekata, K., Yoshida, K., Ohno, S., Tanaka, K., Parada, L.F. Role of Neurotrophin-4/5 in Neural Cell Death during Retinal Development and Ischemic Retinal Injury in Vivo. *Invest Ophthalmol Vis Sci* 46: 669-673, 2005
27. Sarthy, V.P., Pignataro, L., Pannicke, T., Weick, M., Reichenbach, A., Harada, T., Tanaka, K., Marc, R. Glutamate transporter in retinal Muller cells from glutamate/aspartate transporter (GLAST) knockout mice. *Glia* 49. 184-196, 2005
28. Sarthy, V.P., Pignataro, L., Marc, R., Tanaka, K. The contribution of a glial glutamate transporter to GABA synthesis in the retina. *NeuroReport* 15. 1895-1898, 2004
29. Sarthy, V.P., Dudley, V.J., Tanaka, K. Retinal glucose metabolism in mice lacking the L-glutamate/aspartate transporter. *Vis. Neurosci.* 21. 637-643, 2004
30. Huang, Y.H., Tanaka, K., Rothstein J.D., Bergles D.E. Astrocyte glutamate transporters regulate metabotropic glutamate receptor-mediated excitation of hippocampal interneurons. *J. Neurosci.* 24. 4498-4509, 2004.
31. Maekawa, F., Tsukahara, S., Tanaka, K., Ohki-Hamazaki, H. Distributions of two chicken bombesin receptors, bombesin receptor subtype-3.5 (chBRS-3.5) and gastrin-releasing peptide receptor (chGRP-R) mRNA's in chicken telencephalon. *Neuroscience* 125. 569-582, 2004.
32. Maekawa, F., Quah, H.-M.A., Tanaka, K., Ohki-Hamazaki, H. Leptin resistance and enhancement of feeding facilitation by melanin-concentrating hormone in mice lacking bombesin receptor subtype-3. *Diabetes* 53. 570-576, 2004.
33. Chen, W., Mahadomrongkul, V., Berger, U.V., Bassan, M., DeSilva, T., Tanaka, K., Irwin, N., Aoki, C., Rosenberg, P.A. The glutamate transporter GLT1a is expressed in excitatory axon terminals of mature hippocampal neurons. *J. Neurosci.* 24. 1136-1148, 2004
34. Harada, C., Harada, T., Mitamura, Y., Quah, H-M.A., Ohtsuka, K., Kotake, S., Ohno, S., Wada, K., Takeuchi, S., Tanaka, K. Diverse NF-kB expression in epiretinal membranes after human diabetic retinopathy and proliferative vitreoretinopaty. *Mol.*

Vision 10. 31-36, 2004

35. Huang, Y., Dykes Hoberg, M., Tanaka, K., Rothstein J.D., Bergles D.E. Climbing fiber activation of EAAT4 transporters and kainite receptors in cerebellar Purkinje cells. *J. Neurosci.* 24. 103-111, 2004
36. Harada, T., Harada, C., Wang, Y-U., Osaka, H., Amanai, K., Tanaka, K., Takizawa, S., Setsuie, R., Sakurai, M., Sato, Y., Noda, M., Wada, K. Role of ubiquitin carboxy terminal hydrolase-L1 in neural cell apoptosis induced by ischemic retinal injury in vivo. *Am. J. Pathol.* 164. 59-64, 2004
37. Jin, Z.H., Kikuchi, T., Tanaka, K., Kobayashi, T. Expression of GLAST in the developing mouse cochlea. *Tohoku J. Exp. Med.* 200. 137-144, 2003
38. Harada, C., Harada, T., Quah, H.-M. A., Maekawa, F., Yoshida, K., Ohno, S., Wada, K., Parada, L. F., Tanaka, K. Potential role of glial cell line-derived neurotrophic factor receptors in Muller glial cells during light-induced retinal degeneration. *Neuroscience* 122. 229-235, 2003
39. Mitani, A., Tanaka, K. Functional changes of glial glutamate transporter GLT-1 during ischemia: An in vivo study in the hippocampal CA1 of normal mice and of mutant mice lacking GLT-1. *J. Neurosci.* 23. 7176-7182, 2003
40. Voutsinos-Porche, B., Knott, G., Tanaka, K., Quairiaux, C., Welker, E., Bonvento, G. Glial glutamate transporters and maturation of the mouse somatosensory cortex. *Cereb. Cortex* 13. 1110-1121, 2003
41. Iwabuchi, M., Ui-Tei, K., Yamada, Y., Matsuda, Y., Sakai, Y., Tanaka, K., Ohki-Hamazaki, H. Molecular cloning and characterization of avian bombesin-like peptide receptors: New tools for investigating molecular basis for ligand selectivity. *Brit. J. Pharmacol.* 139. 555-566, 2003
42. Mitamura, Y., Harada, T., Harada, C., Ohtsuka, K., Kotake, S., Ohno, S., Tanaka, K., Takeuchi, S., and Wada, K. NF-kB in epiretinal membranes after human diabetic retinopathy. *Diabetologia* 46. 699-703, 2003
43. Okada, T., Yamada, N., Tsuzuki, K., Horikawa, PM., Tanaka, K., and Ozawa, S. Long-term potentiation in the hippocampal CA1 area and dentategyrus plays different roles in spatial learning. *Eur. J. Neurosci.* 17. 341-349, 2003
44. Voutsinos-Porche, B., Bonvento, G., Tanaka, K., Welker, E., Chatton, J.-Y., Magistretti, P.J., Pellerin, L. Glial glutamate transporters mediate a functional metabolic crosstalk between neurons and astrocytes in the mouse developing cortex. *Neuron* 37. 275-286, 2003.
45. Harada, T., Harada, C., Kohsaka, S., Wada, E., Yoshida, K., Ohno, S., Mamada, H. Tanaka, K., Parada L.F., and Wada, K. Microglia-Muller glia interactions control neurotrophic factor productions during light-induced retinal degeneration. *J.*

Neurosci. 22. 9228-9236, 2002.

46. Nishizaki, T., Nagai, K., Nomura, T., Tada, H., Kanno, T., Tozaki, T., Li, X., Kondoh, T., Kodama, N., Takahashi, E., Sakai, N., Tanaka, K., and Saito, N. A new neuromodulator pathway with a glial contribution mediated via A_{2a} adrenergic receptors. *Glia* 39. 133-147, 2002.
47. Katagiru, H., Tanaka, K. and Manabe, T. Requirement of appropriate glutamate concentrations in the synaptic cleft for hippocampal LTP induction. *Eur. J. Neurosci.* 14. 547-553, 2001.
48. Sugiyama, T., Sadzuka, Y., Tanaka, K. and Sonobe, T. Inhibition of glutamate transporter by theanine enhances the therapeutic efficacy of doxorubicin. *Toxicolgy Lett.* 121. 89-96, 2001.
49. Gray, C., Marie, H., Arora, M., Tanaka, K., Boyde, A., Jones, S. and Attwell, D. Glutamate does not play a major role in controlling bone growth. *J. Bone Miner. Res.* 16. 742-749, 2001.
50. Yamada, K., Fukaya, M., Shibata, T., Kurihara, H., Tanaka, K., Inoue, Y. and Watanabe, M. Dynamic transformation of Bergmann glial fibers proceeds in correlation with dendritic outgrowth of cerebellar Purkinje cells. *J. Comp. Neurol.* 418. 106-120, 2000.
51. Hakuba, N., Koga, K., Gyo, K., Usami, S. and Tanaka, K. Exacerbation of noise-induced hearing loss in mice lacking the glutamate transporter GLAST. *J. Neurosci.* 20. 8750-8753, 2000.
52. Fukaya, M., Yamada, K., Nagashima, M., Tanaka, K. and Watanabe, M. Down-regulated expression of glutamate transporter GLAST in Purkinje cell-associated astrocytes of reeler and weaver mutant cerebella. *Neurosci. Res.* 34. 165-175, 1999.
53. Mennerick, S., Shen, W., Xu, W., Benz, A., Tanaka, K., Shimamoto, K., Isenberg, K., Krause, J. E. and Zorumski, C. F. Substrate turnover by transporters curtails synaptic glutamate transients. *J. Neurosci.* 19. 9242-9251, 1999.
54. Watanabe, T., Morimoto, K., Hirao, T., Suwaki, H., Watase, K. and Tanaka, K. Amygdala-Kindled and Pentylenetrazole-Induced Seizures in Glutamate Transporter GLAST-deficient Mice. *Brain Res.* 845. 92-96, 1999.
55. Kojima, S., Nakamura, T., Nidaira, T., Nakamura, K., Ooashi, N., Ito, E., Watase, K., Tanaka, K., Wada, K., Kudo, Y. and Miyakawa, H. Optical detection of synaptically induced glutamate transport in hippocampal slices. *J Neurosci.* **19**. 2580-2588, 1999.
56. Harada, T., Harada, C., Watanabe, M., Inoue, Y., Sakagawa, T., Nakayama, N., Sasaki, S., Okuyama, S., Watase, K., Wada, K. and Tanaka, K. Functions of the two glutamate transporters GLAST and GLT-1 in the retina. *Proc. Natl. Acad. Sci. USA.*

95. 4663-4666, 1998.

57. Hirano, T., Morimoto, K., Yamamoto, Y., Sato, H., Watanabe, T., Sato, K., Sato, S., Yamada, N., Tanaka, K. and Suwaki, H. Time-dependent and regional expression of GABA transporter mRNAs following amygdala-kindled seizures in rats. *Mol. Brain Res.* **54**. 49-55, 1998.
58. Nonaka, M., Kohmura, E., Yamashita, T., Shimada, S., Tanaka, K., Yoshimine, T., Tohyama, M. and Hayakawa, T. Increased transcription of glutamate-aspartate transporter (GLAST/GluT-1) mRNA following kainic acid-induced limbic seizure. *Mol. Brain Res.* **55**. 54-60, 1998.
59. Watase, K., Hashimoto, K., Kano, M., Yamada, K., Watanabe, M., Inoue, Y., Okuyama, S., Kawashima, N., Hori, S., Takimoto, M., Wada, K. and Tanaka, K. Motor discoordination and increased susceptibility to cerebellar injury in GLAST mutant mice. *Eur. J. Neurosci.* **10**. 976-988, 1998.
60. Yamada, K., Watanabe, M., Shibata, T., Tanaka, K. and Inoue, Y. Transient axonal localization of glutamate transporter GLT-1 in developing mouse spinal cord. *J. Neurosci.* **18**. 5714-5722, 1998.
61. Yamashita, H., Kawakami, H., Zhang, Y.-X., Tanaka, K. and Nakamura, S. Effects of amino acid ergot alkaloids on glutamate transport via human glutamate transporter hGluT-1. *J. Neurol. Sci.* **155**. 31-36, 1998.
62. Itoh, M., Watanabe, Y., Watanabe, M., Tanaka, K., Wada, K. and Takashima, S. Expression of a glutamate transporter subtype, EAAT4, in the developing human cerebellum. *Brain Res.* **767**. 265-272, 1997.
63. Maeno-Hikichi, Y., Tanaka, K., Shibata, T., Watanabe, M., Inoue, Y., Mukainaka, Y. and Wada, K. Structure and functional expression of the cloned mouse neuronal high-affinity glutamate transporter. *Mol. Brain Res.* **48**. 176-180, 1997.
64. Shibata, T., Yamada, K., Watanabe, M., Ikenaka, K., Wada, K., Tanaka, K. and Inoue, Y. Glutamate transporter GLAST is expressed in the radial glia-astrocyte of developing mouse spinal cord. *J. Neurosci.* **17**. 9212-9219, 1997.
65. Suh, J.-G., Ichihara, N., Saigoh, K., Nakabayashi, O., Yamanishi, T., Tanaka, K., Wada, K. and Kikuchi, T. An in-frame deletion in peripheral myelin protein-22 gene causes hypomyelination and cell death of the schwann cells in the new trembler mutant mice. *Neuroscience*. **79**. 735-744, 1997.
66. Tanaka, J., Ichikawa, R., Watanabe, M., Tanaka, K. and Inoue, Y. Extra-junctional localization of glutamate transporter EAAT4 at excitatory Purkinje cell synapses. *NeuroReport*. **8**. 2461-2464, 1997.
67. Tanaka, K., Watase, K., Manabe, T., Yamada, K., Watanabe, M., Takahashi, K., Iwama, H., Nishikawa, T., Ichihara, N., Kikuchi, T., Okuyama, S., Kawashima, N.,

Hori, S., Takimoto, M. and Wada, K. Epilepsy and exacerbation of brain injury in mice lacking the glutamate transporter GLT-1. *Science*. **276**. 1699-1702, 1997.

68. Yamada, K., Wada, S., Watanabe, M., Tanaka, K., Wada, K. and Inoue, Y. Changes in expression and distribution of the glutamate transporter EAAT4 in developing mouse Purkinje cells. *Neurosci. Res.* **27**. 191-198, 1997.
69. Hagiwara, T., Tanaka, K., Takai, S., Maeno-Hikichi, Y., Mukainaka, Y. and Wada, K. Genomic organization, promoter analysis, and chromosomal localization of the gene for the mouse glial high-affinity glutamate transporter Slc1a3. *Genomics*. **33**. 508-515, 1996.
70. Maeno, H., Yoshimura, R., Fujita, S., Su, Q., Tanaka, K., Wada, K. and Kiyama, H. Cloning and characterization of the rat neurotensin receptor gene promoter. *Mol. Brain Res.* **40**. 97-104, 1996.
71. Nakayama, T., Kawakami, H., Tanaka, K. and Nakamura, S. Expression of three glutamate transporter subtype mRNAs in human brain regions and peripheral tissues. *Mol. Brain Res.* **36**. 189-192, 1996.
72. Shibata, T., Watanabe, M., Tanaka, K., Wada, K. and Inoue, Y. Dynamic changes in expression of glutamate transporter mRNAs in developing brain. *NeuroReport*. **7**. 705-709, 1996.
73. Yamada, K., Watanabe, M., Shibata, T., Tanaka, K., Wada, K. and Inoue, Y. EAAT4 is a post-synaptic glutamate transporter at Purkinje cell synapses. *NeuroReport*. **7**. 2013-2017, 1996.
74. Yamashita, T., Kohmura, E., Yuguchi, T., Shimada, S., Tanaka, K., Hayakawa, T. and Tohyama, M. Changes in glutamate/aspartate transporter (GLAST/GluT-1) mRNA expression following facial nerve transection. *Mol. Brain Res.* **38**. 294-299, 1996.
75. Mukainaka, Y., Tanaka, K., Hagiwara, T. and Wada, K. Molecular cloning of two glutamate transporter subtypes from mouse brain. *Biochem. Biophys. Acta*. **1244**. 233-237, 1995.
76. Suh, J. G., Yamanishi, T., Matsui, K., Tanaka, K. and Wada, K. Mapping of the gracile axonal dystrophy (gad) gene to a region between D5Mit197 and D5Mit113 on proximal mouse chromosome 5. *Genomics*. **27**. 549-551, 1995.
77. Takai, S., Yamada, K., Kawakami, H., Tanaka, K. and Nakamura, S. Localization of the gene (SLC1A3) encoding human glutamate transporter (GluT-1) to 5p13 by fluorescence in situ hybridization. *Cytogenet Cell Genet.* **69**. 209-210, 1995.
78. Yamashita, H., Kawakami, H., Zhang, Y.-X., Hagiwara, T., Tanaka, K. and Nakamura, S. Inhibition by folded isomers of L-2-(carboxycyclopropyl)glycine of glutamate uptake via the human glutamate transporter hGluT-1. *Eur. J. Pharmacol.*

289. 387-390, 1995.

79. Yamashita, H., Kawakami, H., Zhang, Y.-X., Tanaka, K. and Nakamura, S. Neuroprotective mechanism of bromocriptine. *Lancet*. **346**. 8985: 1305, 1995.
80. Kawakami, H., Tanaka, K., Nakayama, T., Inoue, K. and Nakamura, S. Cloning and expression of a human glutamate transporter. *Biochem. Biophys. Res. Commun.* **199**. 171-176, 1994.
81. Otori, Y., Shimada, S., Tanaka, K., Ishimoto, I., Tano, Y. and Tohyama, M. Marked increase in glutamate-aspartate transporter (GLAST/GLuT-1) mRNA following transient retinal ischemia. *Mol. Brain Res.* **27**. 310-314, 1994.
82. Suh, J. G., Oda, K., Tanaka, K., Yorifuji, H., Tomita, T. and Wada, K. Pathophysiological study of axonal degeneration in the Gracile Axonal Dystrophy (gad) mutant mice. *Biomed. Res.* **15**. 241-246, 1994.
83. Tanaka, K. Pharmacological characterization of a cloned rat glutamate transporter (GluT-1). *Mol. Brain Res.* **21**. 1-2: 167-170, 1994.
84. Tanaka, K. Expression cloning of a rat glutamate transporter. *Neurosci. Res.* **16**. 149-153, 1993.
85. Tanaka, K. Cloning and expression of a glutamate transporter from mouse brain. *Neurosci. Lett.* **159**. 1-2: 183-186, 1993.
86. Koyano, K., Tanaka, K. and Kuba, K. A patch-clamp study on the muscarine-sensitive potassium channel in bullfrog sympathetic ganglion. *J. Physiol.* **454**. 231-246, 1992.
87. Tanaka, K., Koyano, K. and Kuba, K. A muscarine-activated voltage-independent K+ channel in cultured bullfrog sympathetic neurones. *Neurosci. Lett.* **121**. 191-193, 1991.
88. Tanaka, K., Masu, M. and Nakanishi, S. Structure and functional expression of the cloned rat neurotensin receptor. *Neuron*. **4**. 847-854, 1990.
89. Yokota, Y., Sasai, Y., Tanaka, K., Fujiwara, T., Tsuchida, K., Shigemoto, R., Kakizuka, A., Ohkubo, H. and Nakanishi, S. Molecular characterization of a functional cDNA for rat substance P receptor. *J. Biol. Chem.* **264**, 17649-17652, 1989.
90. Tanaka, K. and Kuba, K. The Ca^{2+}-sensitive K^{+}-currents underlying the slow afterhyperpolarization of bullfrog sympathetic neurones. *Pflügers Archiv* **410**, 234-242, 1987.
91. Tanaka, K., Minota, S., Kuba, K., Koyano, K. and Abe, T. Differential effects of apamin on Ca^{2+}-dependent K^{+} currents in bullfrog sympathetic ganglion cells. *Neurosci. Lett.* **69**. 233-238 1986.